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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,086	05/30/2006	Dominique Jean-Pierre Mabire	PRD-2121 USPCT	1676

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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

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01/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,086	MABIRE ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6,10-16,18,19,21,22 and 24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4, 6, 10-16, 18, 19, 21, 22 & 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11, 18, 19, 21, 22, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not provide reasonable enablement for a method to enhance chemotherapy effectiveness (claims 10, 18, 21, 24), or radiotherapy effectiveness (claims 11, 19, 22, 25) with the claimed compounds. The specification states that present compounds are PARP inhibitors and extrapolates therefrom to assert the claimed compounds will treat the above-recited conditions.

Substantiation of the method of use is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). See *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding testing types needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instant method claims based solely on anti-hypolipidemic activity. The state of the art, as exemplified by the references discussed supra, is indicative of the requirement for undue experimentation.

Thus, ability of a compound that modulates kinase activity to prevent or ameliorate all of the diseases/conditions recited by the present claims remains open to proof.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover pharmaceutical methods using millions of 6-substituted 2-quinolinones and 2-quinoxalinone compounds. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as pharmaceutical arts.

(b) Scope of the diseases covered. The diseases construed by the claims are as described above. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as pharmaceutical arts. The specification

fails to identify the results of treatment with the methods of this invention and how such results would be recognized.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

Tentori, et al., Pharmacol. Res., Vol. 52, # 1, July 2005, 25-33, discussing chemopotentiation by PARP inhibitors in cancer therapy, express toxicity concerns:

> A major concern deriving from the treatment of cancer patients with PARP inhibitor combined with chemotherapy remain systemic toxicity, since inhibition of DNA repair in normal tissues may increase sensitivity to the genotoxic damage provoked by the antitumor agents. In particular, the combination of PARP inhibitor and TMZ has shown to be toxic also

> against nonproliferating cells. Finally, due to the involvement of PARP-1 in maintenance of genomic stability treatment with repeated cycles of PARP inhibitors and chemotherapy might induce genomic instability in normal cells increasing the chances of secondary tumors. Although the incidence of toxicity toward normal differentiated tissues and the risk-benefit ratio will be addressed in clinical trials, efforts should be made to counteract resistance to chemotherapy selectively in tumor cells.

Albert, et al., Clin. Can. Res. 13, 3033-3042, May 15, 2007, discuss a single PARP inhibitor to enhance cell death and improve tumor growth delay in a single irradiated lung cancer model, and report the need for further research:

> [W]e used PARP-1 inhibitor ABT-888 in combination with radiation in non-small cell lung cancer models. ABT-888 is a novel potent small-molecule PARP-1 inhibitor that is currently in a dose escalation phase 0 clinical trial for refractory solid tumors and lymphoid malignancies. However, the use of this agent with radiation has not been previously explored. Our data provide evidence to support the efficacy and feasibility of combining ABT-888 with radiotherapy, and also provide further evidence supporting the use of PARP-1 inhibitors to potentiate the effects of radiation. Future clinical studies are needed to determine the efficacy of ABT-888 in combination with radiotherapy in lung cancer patients.

Ability of an agent that exhibits the specific activities shown in the specification to evidence the activities recited by the claims remains open to further study and proof.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) held a claim not enabled when the claim covers multiple embodiments but the specification fails to enable all embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." The claims here cover any chemotherapy or radiotherapy and do not enable them all.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the embodiments. "Thus, in order

to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." The claims here cover any chemotherapy or radiotherapy and do not enable them all.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.
6. **Skill of those in the art:** Tentori and Albert call into question ability of a single class of compounds to effectively exhibit the all activities the claims construe. These references confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles referenced above, indicates the requirement for undue experimentation. Thus, the ability of an agent that exhibits the specific activities shown in the specification to treat all of the diseases construed by the present claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 6, 10-16, 18, 19, 21, 22 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which the specification does not describe in such a way as to reasonably convey to one skilled in the relevant art that the inventors, when the application was filed, had possession of the claimed invention. This is a new matter rejection.

There is no support in the application as filed for the added proviso in claim2 "that when n is 0, X is N, R2 is hydrogen, R3 is a group of formula (b-1), Z is the heterocyclic ring system (c-2) or (c-4) wherein said heterocyclic ring system Z is attached to the rest of the molecule with a nitrogen atom, and R10 is hydrogen; then R4 is other than hydrogen, C1-6alkyl or pyridinyl." limitation in claim 152 of "multiple sclerosis, rheumatoid arthritis or allograft rejection." Applicants point to no support for the added proviso and the examiner finds none.

Introduction of claim changes which involve claim narrowing by introducing elements or limitations not supported by the as-filed disclosure is a violation of 35 USC 112, first paragraph, written description requirement. See *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus; it does not "reasonably lead" one skilled in the art to any particular species or sub-genus).

The application as filed does not disclose the proposed sub-genus in *ipsis verbis*. *Ipsis verbis* disclosure is not necessary to satisfy section 112 written description requirement. Instead, the disclosure need only reasonably convey to persons skilled in the art that applicant had possession of the subject matter in question. *In re Edwards*, 196 USPQ 465, 467 (CCPA 1978). In other words, the question is whether the present "application provides adequate direction which reasonably [would lead] persons skilled in the art" to the sub-genus of the proposed claim. As was remarked by the Court of Customs and Patent Appeals more than forty years ago and remains true today:

> It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail . . . to be confronted simply by a large number of unmarked trees. [Applicants] are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

In re Ruschig, 154 USPQ 118, 122 (CCPA 1967).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 6, 10-16, 18, 19, 21, 22 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2: R8 is defined, but there is no R8 in the compound of formula (I). R3 is defined in the proviso as "a group of formula (b-1)," but there is no group of that formula in the claim. It is not understood what is meant in the proviso by "Z is attached to the rest of the molecule with a nitrogen atom." It is not understood what is meant by "the rest of the molecule" and there is no antecedent basis for this phrase. It is not possible

for either (c-3) or (c-4) to be attached by nitrogen, because the ring nitrogen in both rings has a hydrogen substituent. It is not possible for an extra nitrogen to be interposed between the Z moiety and R3, because such a structure is not provided for by formula (I) and such a structure would have unsatisfied nitrogen valences.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

Cecilia M. Jaisle
1/6/2009